REMARKS/ARGUMENTS

The reply filed on May 20, 2008 has been alleged by the Examiner not to comply with 37 CFR 1.21(c) in that Applicant's amendments to claims 15-20 and 22 are not believed to match that of the previously entered amendment filed on August 22, 2007. Claims 1-22 were initially examined in the above-identified application. Claims 7-14 were previously withdrawn from consideration by the Examiner as being directed to a non-elected invention. Claims 7 through 14 were subsequently cancelled without prejudice to Applicant's right to prosecute the subject matter encompassed by the claims in a related, co-pending application in the response filed August 22, 2007. Further, claims 1 through 6 were also cancelled in the August 22, 2007 response without prejudice to Applicant's right to prosecute the subject matter of the encompassed by the claims in a related co-pending application. Claims 15 through 20 and 22 were amended and claim 23 was added. The Examiner issued a Notice of Non-compliant Response November 14, 2007, the Examiner believing that the amendments to claims 15-20 and 22 were amended so as to not encompass the invention elected in the earlier response to the Request for Restriction. Applicant responded to the Notice May 14, 2008, but apparently used the claims from the application as filed instead of the amended claims filed with the August 22, 2007 response that were entered in the May 14, 2008 Notice of Non-compliant Response. Applicant's representative apologizes for the inadvertent error and has re-presented amendments to the claims based on those claims filed and entered in the May 14, 2008 Notice. Support for the amendments to claims 15, 20 and 21 in the present response is identified in the following remarks. No new matter is added by these amendments. Reconsideration of the claims pending in the application is respectfully requested.

In the Notice of Non-compliant response dated February 22, 2007, the Examiner considered the amendments to claim 15 and the amendments to claims 16-23 as directed to an invention that was not elected subject matter for which Applicant received a first office action. The Examiner believes that claim 15, as amended, is directed to an invention that is independent

or distinct from the invention originally claimed and elected with traverse. In particular, the Examiner has characterized the elected invention examined in the first office action, and specifically claims 15-22, as being drawn to a method for inducing the activation and proliferation of Natural Killer cells (NK cells) comprising contacting the NK cells with a dendritic cell that can induce the activation and proliferation of the NK cells. Amended claim 15 is alleged by the Examiner to be directed to a method for inducing the activation and proliferation of NK cells comprising contacting a human cell population comprising NK cells and monocytic dendritic precursor cells with an effective amount of GM-CSF and IL-15 to form immature dendritic cells and further contacting the cell population with a dendritic cell maturation agent to produce a mature dendritic cell which can induce the activation and proliferation of the NK cells in the cell population. The Examiner does not believe that the claims as amended are drawn to contacting a NK cell with a dendritic cell capable of inducing activation and proliferation of NK cells. As such, the Examiner has entered amended claims 15-22 and new claim 23, but has withdrawn the claims from prosecution. The withdrawal of the claims would leave no claim pending in the application that are drawn to the elected invention so the present Notice was issued.

Applicants do not believe that the invention as encompassed by now withdrawn claims 15-23 are directed to a non-elected invention, but in order the further expedite prosecution of the application, claim 15 has been amended to recite "contacting a human NK cell with a dendritic cell that can induce the activation and proliferation of NK cells, wherein the dendritic cell is a mature dendritic cell that has been produced from a monocytic dendritic cell precursor by contact with an effective amount of granulocyte macrophage-colony stimulating factor (GM-CSF) and interleukin 15 (IL-15)". The current amendment is believed to encompass the subject matter of the elected invention of contacting NK cells with a mature dendritic cell capable of inducing activation and proliferation. In the present claim the mature dendritic cell has been produced by previously contacting monocytic dendritic cell precursors with GM-CSF and IL-15. Such mature dendritic cells express increased levels of CD80 and CD86 as compared with mature dendritic cells produced from monocytic dendritic cell precursors cultured in the presence

of GM-CSF and IL-4. Applicant respectfully requests that the Examiner reconsider the withdrawal of claims 15-23 and continue substantive examination of the application.

Remarks are provided below to respond the rejections set forth in the February 22, 2007 Official Action. The remarks are modifications of those filed previously, but are based on the claims as set forth above. The Examiner is respectfully requested to reconsider the rejections of claims 15-23 in view of the above amendments and the remarks below.

Rejections Under 35 U.S.C. §112:

Claims 1-2, 4-5, and 15-16 were rejected under 35 U.S.C. §112, first paragraph, in the Official Action dated February 22, 2007 because the Examiner believed that while the specification was enabling for mature dendritic cells derived from monocytic dendritic precursor cells cultured in GM-CSF and IL-15 that exhibit increased expression of CD80 and CD86 as compare to mature dendritic cells cultured in the presence of GM-CSF and IL-4 and were capable of increasing the proliferation of NK cells in culture by at least 10 fold or at least 30 fold after at least 7 days of co-culture, did not reasonably provide enablement for any dendritic cell with the claimed phenotypes of increased expression of CD80 and CD86 as compared to mature dendritic cells cultured in the presence of GM-CSF and IL-4 and the capacity to increasing the proliferation of NK cells in culture by at least 10 fold or at least 30 fold after at least 7 days of co-culture. Further, the Examiner did not believe that the specification enabled any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Furthermore, the Examiner alleged that the specification failed to provide any guidance as to alternative culture conditions for producing immature or mature dendritic cells that shared the same phenotype as the mature dendritic cells produced by culture of low-adherence dendritic precursor cells in GM-CSF and IL-15. The Examiner also alleged that the specification failed to provide any guidance as to whether dendritic cells with the claimed phenotype could be isolated from any mammal, or under what conditions or isolation techniques.

Applicant does not agree with the Examiner's characterization of the specification or the analysis of the prior art, but in order to further expedite prosecution of certain subject matter disclosed and claims in the specification Applicant cancelled claims 1 through 6 without prejudice in the response filed August 22, 2007 and amended claim 15 has been currently amended. Therefore, the rejection as to claims 1 through 6 is moot. Claims 15 has been amended to recite "[a] method for inducing the activation and proliferation of natural killer (NK) cells, comprising: contacting a NK cell with a dendritic cell that can induce the activation and proliferation of NK cells, wherein the dendritic cell is a mature dendritic cell that has been produced from a monocytic dendritic cell precursor by contact with an effective amount of granulocyte-monocyte colony stimulating factor (GM-CSF) and interleukin 15 (IL-15)." Further, claim 16 has been amended to recited "the dendritic cell" of claim 15. Applicant believes that the method of amended claim 15 and previously presented claim 16 is fully supported by the specification as filed. In particular, the Examiner is directed, for example, to pages 11 through 14 and Example 4 wherein various methods for the isolation and culture of a human cell population comprising NK cells and dendritic cells that have been cultured in the presence of GM-CSF and IL-15 is described. Subsequent to the steps in the recited method the number of NK cells in the cell population have increased substantially above the number that would have been obtained if the NK cell was cultured with a dendritic cell that had been produced in the presence of the standard cytokine mixture of GM-CSF and IL-4. The NK cells in the cell population have been activated.

Applicant respectfully requests that the Examiner reconsider claims 15 and 16 and withdraw the rejection under 35 U.S.C. § 112, first paragraph, in view of the above amendments and remarks.

Claims 4-5 and 22 were rejected in the Official Action dated May 22, 2207 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4 and 5 have been cancelled without prejudice in the response dated August 22, 2007 and entered by the Examiner.

As to Claims 15-22, the Examiner believed that the claims were unclear and indefinite in that they encompassed contact between the NK cells and dendritic cells *in vivo*, see dependent claim 19 in particular. For *in vivo* contact, the Examiner has alleged that the claims are confusing in that no active steps for administering either a population of dendritic cells and/or a population of NK cells to a mammal are recited in the claims. Thus, the Examiner concludes that it is unclear whether the hand of man is actually part of the *in vivo* method and that the metes and bounds of the claims cannot be determined.

The Examiner further has noted that Claim 22 recites the method of claim 21 "wherein the population of leukocytes are further contacted with antigen presenting dendritic cells." The Examiner alleges that it is unclear whether these dendritic cells are different from the dendritic cell with which the NK cell is contacted in the base claim, claim 15.

Without acquiescing to any remark of the Examiner, Applicant amended claims 19 and 22, and added new claim 23 in the response dated August 22, 2007 and entered by the Examiner. In particular, claim 19 was amended to delete *in vivo* contact of the NK cells with mature dendritic cells. Further, claim 15 has been amended above to recite "a method for inducing the activation and proliferation of natural killer (NK) cells, comprising: contacting a human NK cell with a dendritic cell that can induce the activation and proliferation of NK cells, wherein the dendritic cell is a mature dendritic cell that has been produced from a monocytic dendritic cell precursor by contact with an effective amount of granulocyte-monocyte colony stimulating factor (GM-CSF) and interleukin 15 (IL-15)." As such, the NK cells and the mature dendritic cells produced by the method are in the same population. Claim 21 as amended in the August 22, 2007 recites that the cell population comprising the NK cells and the monocytic dendritic cell precursor cells contacted with the various cytokines of the method can further be contacted with an additional population of cells comprising NK cells. Claim 22 as amended in the August 22, 2007 response recites that the population of leukocytes of claim 21 can be further contacted with a population of antigen presenting dendritic cells and new claim 23 recites that the NK cells in the method according to claim 15 "are further contacted with an effective amount of a desired antigen." Claims 20 and 21 are above amended to delete the phrase "cell population

comprising" to make the claims consistent with amended claim 15. Applicant believes that each of these claims is fully supported by the specification as filed.

In particular, support for amended claim 15 can be found as set forth above in the rejection under 35 U.S.C. § 112, first paragraph. Support for amended claim 19 can be found in original claim 19. Pages 13 and 14, and Example 7, for example, provide support for amended claims 21 and 22 and new claim 23.

Applicant respectfully requests the Examiner consider and withdraw the rejection of claim 22 under 35 U.S.C. § 112, second paragraph in light of the amendments and remarks above.

Rejections Under 35 U.S.C. §102

Claims 1-6 were rejected under 35 U.S.C. §102(b) as being anticipated by Mohamadzadeh *et al.* (*J. Exp. Med.* 194:1013-1019, 2001). The Examiner alleged that Mohamadzadeh *et al.* teaches the preparation of immature dendritic cells by culturing monocytes in the presence of either GM-CSF and IL-15 or GM-CSF and IL-4. Further, the Examiner alleges that Mohamadzadeh *et al.* teaches maturation of the dendritic cells by treatment with LPS and that the mature dendritic cells produced from the culture of moncytic precursors in GM-CSF and IL-15 exhibited expression of CD1a, and high levels of CD80 and CD86. It has been noted by the Examiner that Mohamadzadeh *et al.* did not do a direct comparison of the phenotype of the IL-15 dendritic cells with the IL-4 dendritic cells, but that the IL-15 dendritic cells of Mohamadzadeh *et al.* were produced using the same culture conditions, *i.e.*, culture in IL-15 and GM-CSF, and appear to express the same markers. The Examiner has also noted that while Mohamadzadeh *et al.* did not test the ability of these cells to induce the proliferation or activation of NK cells, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent."

Applicant does not acquiesce to any comment of the Examiner regarding the teaching of Mahamadzadeh *et al.*, but to further expedite prosecution of certain subject matter

disclosed and claimed in the present application claims 1 through 6 were cancelled without prejudice in the response filed August 22, 2007. As such, this rejection is moot.

Claims 1-6 and 15-22 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 01/85920 A2, (Banchereau *et al.*). The Examiner alleged that Banchereau *et al.* taught the preparation of immature dendritic cells by culturing dendritic cell precursors in the presence of GM-CSF and IL-15, and the maturation of the dendritic cells by treatment with LPS or CD40L. The Examiner further alleges that Banchereau *et al.* taught that the mature dendritic cells produced from the culture of dendritic precursors in GM-CSF and IL-15 exhibited expression of CD1a, and high levels of CD80 and CD86 and that the administration of the mature IL-15 dendritic cells to a patient to induce an immune response, where the IL-15 dendritic cells have further been exposed to antigen. The Examiner noted that while Banchereau *et al.* did not do a direct comparison of the phenotype of the IL-15 dendritic cells with dendritic cells produced from culture in GM-CSF and IL-4, the IL-15 dendritic cells of Banchereau *et al.* were produced using the same culture conditions, i.e. culture in IL-15 and GM-CSF, and appear to express the same markers. Further, the Examiner also noted that while Banchereau *et al.* did not test the ability of these cells to induce the proliferation or activation of NK cells, "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent."

Applicant does not acquiesce to any comment of the Examiner regarding the teachings of Banchereau *et al.*, but in order to further expedite prosecution of certain methods disclosed and claimed in the application have cancelled claims 1 through 6 without prejudice. Therefore, the rejection of claims 1 through 6 under 35 U.S.C. § 102(b) as anticipated by Banchereau *et al.* is moot.

As to the methods claims 15-22, the Examiner has noted that the methods as claimed contain a single method step, "contacting the NK cells with a dendritic cell." The Examiner alleges that dependent claim 19 clarifies that the "contact" can be "in vivo." Banchereau *et al.* is alleged by the Examiner to teach the *in vivo* administration of mature IL-15

dendritic cells to a mammal to induce an immune response and as such, as Mammals comprise NK cells, such *in vivo* administration of dendritic cells constitutes contact of dendritic cells with NK cells. The Examiner does note that Banchereau *et al.* teach the stimulation of T cells, not NK cells, but that it is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable.

Applicant does not acquiesce to any comment of the Examiner as to the teaching of Banchereau *et al.*, but in order to further expedite prosecution of certain methods disclosed in the present application have amended claim 15 to recite "[a] method for inducing the activation and proliferation of natural killer (NK) cells, comprising: contacting a human cell population comprising NK cells and monocytic dendritic precursor cells with an effective amount of granulocyte-monocyte colony stimulating factor (GM-CSF) and interleukin 15 (IL-15) to form immature dendritic cells; and contacting the cell population comprising the NK cells and the immature dendritic cells with an effective amount of a dendritic cell maturation agent under conditions suitable for maturation of the dendritic cell, such that the mature dendritic cell induces the activation and proliferation of the NK cells in the cell population." Further, claim 19 has been amended to delete the recitation of *in vivo*. The method of the invention now comprises the contact of the monocytic dendritic cell precursors and the NK cells with GM-CSF and IL-15 followed by contact with the dendritic cell maturation agent. All of the steps take place outside of the body. Banchereau *et al.* do not disclose or suggest such a method. Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claims 1, 6, 15, and 18-21 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,849,452 (2/1/05), (Zitvogel *et al.*). The Examiner has alleged that Zitvogel *et al.* teach methods for inducing the activation of NK cells comprising contacting resting NK cells with mature dendritic cells *in vitro* or *ex vivo*. Zitvogel *et al.* is further alleged by the Examiner to teach that the NK cells and dendritic cells can be contacted *in vivo* by administering the dendritic cells to a mammal and that contact between the NK cell and dendritic cell can lead to the proliferation of the NK cell. In addition, the Examiner has alleged that Zitvogel *et al.* teach that the dendritic cells express IL-12, TNF-alpha, IL-15, and IFN α/β and

that the NK cells can be population of leukocytes prepared by leukopheresis, or a highly enriched population of resting NK cells comprising more than 70% resting NK cells. The Examiner concluded that by teaching all the limitations of the claims as written, Zitvogel *et al.* anticipates the instant claims.

Applicant does not believe that Zitvogel *et al.* anticipates the present invention as claimed. In particular, amended claim 15 is directed to contacting a cell population comprising NK cells with a dendritic cell, wherein the dendritic cell has been produced by contacting monocytic dendritic precursor cells with GM-CSF and IL-15. These culture conditions provide a mature dendritic cell that can induce the NK cells that exist alone or in a cell population, and further any subsequent NK cells that can be added, to proliferate and to become activated. Further, claims 18 through 21 have been amended. Claim 18 has been amended to recite that the dendritic cell that can induce the proliferation and activation of the NK cells is a mature dendritic cell. As above, claim 19 has been amended to delete *in vivo*. In addition, claims 20 and 21 have been amended the clarify that the NK cells of claim 15 can be substantially isolated or are provided as a population of leukocytes. The cell population can also be contacted with a population of mature dendritic cells that have been contacted with a predetermined antigen or with the predetermined antigen itself. In the first method, a population of dendritic cells can be produced by any number of methods that have been contacted and present the predetermined antigen. In the second method, the predetermined antigen is contacted, with for example, the immature dendritic cells and a dendritic cell maturation is added to mature the dendritic cell while it uptakes and processes the antigen for presentation. As such, Zitvogel does not anticipate or suggest the invention as presently claimed.

The Examiner is respectfully requested to reconsider and withdraw the rejection of claim 15 and 18 through 21 under 35 U.S.C. § 102(e) as anticipated by Zitvogel *et al.* in light of the above amendments and remarks.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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